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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/540,843	03/31/2000	Barbara A. Gilchrest	0054.1088-015	2644

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/540,843	GILCHREST ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/15/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,19,20,23,25,26,29,32,51,52,57,58,69,71,72,75-79,81-83,85,86,88,89,93-95,98-107 and 110 113.* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continuation of Disposition of Claims: Claims pending in the application are 1-11,13-17,19,20,23,25,26,29,32,51,52,57,58,69,71,72,75-79,81-83,85,86,88,89,93-95,98-107 and 110-113.

DETAILED ACTION

Non-Final Rejection

Claims 1-11,13-17, 19, 20, 23, 25, 26, 29, 32, 51, 52, 57, 58, 69, 71, 72, 75-79, 81-83, 85, 86, 88, 89, 93, 94, 95, 98-107, and 110-113 are pending.

Applicants' traversal, the amendment to claims 1, 77, 81, and 88, the cancellation of claims 12, 18, 21, 22, 24, 27, 28, 30, 31, 33-50, 53-56, 59-68, 70, 73, 74, 80, 84, 87, 90-92, 96, 97, 108, and 109 in paper filed on 12/15/03 is acknowledged and considered.

NOTE: The status of claims 2, 4, 6, 7, 8, 13, 14, 19, 20, 25, 26, 29, 51, 57, 69, 71, 72, 75, 76, 78, 79, 82, 83, 85, 86, 89, 93, 94, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 110, 112, and 113 is improper and the status of the claims should be listed as (previously presented).

In addition, Claim 85 was amended in paper filed on 12/15/03 and not marked as currently amended. See paper filed on 5/20/03. The word "dimers" on line 4 of the claim is now misspelled (dimmers).

In the response to this instant office action Applicants are reminded to follow revised 37 CFR 1.121. See 68 Fed. Reg. 38611 (June 30, 2003) or website http://www.uspto.gov/web/patents/ifw/.

The indicated allowability of claims 1-7, 9-11, 13, 20, 23, 25, 26, 29, 32, 51, 52, 58, 69, 71, 72, 75-79, 81, 82, 83, 86, 88, 94, 95, 98-106, 107, and 111-113 are withdrawn

in view of the newly discovered patent application by applicants that requires a new provisional double patenting rejection and new objection and/or rejections to claims 7, 9-11, 13, 51, 52, 58, 69, 71, 72, 106, 107, and 113.

Priority

This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. A statement reading, "This application is a CIP of Application No. 09/048,927 filed March 26, 1998 which is a CIP of US National Phase of PCT/US96/08386 filed June 3, 1996 and assigned US Application No. 08/952,697 which is a CIP of Application No, 09/467,012 filed June 6, 1995 now US Patent No. 5/955,059." follows the title of the invention or as the first sentence of the specification. However, the current status of the nonprovisional parent applications referenced is not included.

Appropriate correction is required.

Information Disclosure Statement

The fee set forth in § 1.17(p).was charged to Deposit Account. See MPEP 609, 37 CFR 1.97.

Claim Objections

Claim 85 is objected to because of the following informalities: the word "dimer" is misspelled on line 4. Appropriate correction is required.

Claim 113 is objected to because of the following informalities: the phrase "treating inhibiting" is grammatically incorrect on line 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 85 and 89 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an effective amount of a composition selected from the group consisting of DNA dinucleotides and DNA dimers in the claimed method, does not reasonably provide enablement for making and using other dinucleotide or dimer in the claimed method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The state of the art for administering oligonucleotides teaches that relatively little is known about the *in vivo* behavior of oligonucleotide (Plenat, Molecular Medicine, Vol. 1, pp. 250-275) and extrapolation from *in vitro* studies to predict pharmacokinetics and effects in a mammal are difficult and inappropriate (abstract). Furthermore, Plenat teaches that, "oligonucleotides in their natural phosphodiester form are subject to rapid degradation in the blood or intracellular fluid by exonuclease and endonucleases (page

250)." In addition, Plenat teaches that oligonucleotides are inhibited from reaching the target by side effects, which result from interactions with cellular or extracellular proteins as well as complementarity with mRNAs for a protein other than the target (page 252).

Furthermore, the art of record further supports the unpredictability of oligonucleotide therapy by displaying conflicting results using the specific oligomer, e.g. TTAGGG (SEQ ID NO: 11 in instant application) for inhibiting cell proliferation. Ohnuma et al. tested the cell growth inhibitory effects of telomere-mimic oligomer, using TTAGGGn, where n=1, 2, 3 or 4 on 8 human tumor cell lines (abstract). Ohnuma displays that only the 18-mer (n=3) and the 24-mer (n=4) inhibited cell growth in some of the cell lines and the 6-mer and 12-mer did not displays any cell growth inhibitory effect (page 2457, table 1). However, Page showed that, "TAG-6 can inhibit telomerase activity *in vitro* and this compound was known to have anti-proliferative effects *in vitro* and *in vivo* against a Burkitt's lymphoma cell line and xenographs in nu/nu C57 black mice (page 41)." In addition, Pages teaches that, "cytotoxicity varies among several types cell types tested with specific cells exhibiting a sensitivity not found in two other types of cell lines (page 47)." Thus, the state of the art teaches that oligonucleotide technology is characterized by a high degree of unpredictability.

The specification provides working examples 1-16 (pages 20-41) a brief description of each example follows.

Examples 1-10 use a dinucleotide pTpT (T2). Examples 1-3 display that using T2 could inhibit different types of cancer cell lines *in vitro*. Examples 4-5 display that using T2 could inhibit different types of normal neonatal cell lines *in vitro*. Example 6 is an *in vivo* comprising topically administering T2 showing that epidermal cell proliferation

could be inhibited. Example 7 displays that T2 increases p53 transcription activity in vitro. Example 8 displays that T2 enhances DNA repair via p53 in neonatal human skin cells in vitro. Example 10 displays that T2 induces IL-10 in human keratinocytes, which is likely to cooperate with TNFalpha to inhibit contact hypersensitivity in vitro.

Example 11 uses several different oligonucleotides (SEQ ID NOs: 1, 2, 3, 4, and 6, including T2) and displays that SEQ ID NOs: 1-4 stimulates melanogenesis in human melanocytes *in vitro*. However, SEQ ID NO: 6 did not stimulate melanogenesis in vitro. Example 12 uses T2 and several oligonucleotides (SEQ ID NOs: 5 and 8-12) and displays that SEQ ID NOs: 5, 8, and 10 were highly melanogenic in vitro, while the reverse complimentary sequence of SEQ ID NO: 11 (SEQ NO: 12) were less active (figure 18). However, SEQ ID NOs: 9 and 10 did not produce significant change in pigment content. Furthermore, Example 12 displays that SEQ ID NO: 1 and T2 can penetrate the skin barrier and produce *in vitro* UV-mimetic effects *in vivo*. In addition, Example 12 displays that oligonucleotide sequence plays a role in determining it melanogenic activity. In addition, Example 12 displays that 5' phosphate is required for efficient uptake.

Example 14 displays that T2 reduced UV-induced mutations *in vivo* and suggest that topical application could be used to lower the mutation rate in carcinogen-exposed skin. Example 15 tested oxidative damage by treating primary newborn fibroblast *in vitro* with T2. The results displayed that T2 increase cell survival. Example 16 tested DNA repair capacity in newborn, young adult, and older adult fibroblast by using either T2 or SEQ ID NO: 1 containing a 5' phosphate. Pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) resulted in up regulated constitutive of UV-induced proteins (p53, p21,

XPA, RPA, ERCC/PF, PCNA). In addition, pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) increased the removal of photoproducts by 30-60 percent.

The specification provides sufficient guidance for using a DNA oligonucleotide, wherein said deoxynucleotides is approximately 2-200 nucleotides in length, and wherein the DNA oligonucleotide comprises a phosphodiester backbone in the claimed methods. However, the breadth of the claims read on using any type of oligonucleotide (DNA, RNA, etc.) and the specification does not provide sufficient guidance for using any RNA oligonucleotide in the claimed methods. The chemical properties and the biological activity of DNA oligonucleotides are distinct from the chemical properties and biological activity of RNA oligonucleotides. The art of record teaches the unpredictability of making and using DNA oligonucleotides and the specification does not provide sufficient guidance to reasonably correlate from making and using the DNA oligonucleotides taught in the specification to making and using any RNA oligonucleotide embraced by the claimed invention. The art of record is absent for how to make and use RNA oligonucleotides in the claimed method. In view of the lack of guidance provided by the specification for making and using any oligonucleotide in the claimed methods, it would take one skilled in the art an undue amount of experimentation to practice the full scope claimed invention. Thus, the specification does not commensurate with the full scope of the claimed invention.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable making and using an effective amount of a composition selected from the group consisting of DNA dinucleotides and DNA dimers in the claimed method.

Given that oligonucleotide therapy wherein any oligonucleotide is employed to treat a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to an oligonucleotide therapy effect produced by any oligonucleotide cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of oligonucleotide therapy.

Applicant's arguments filed 12/15/03 have been fully considered but they are not persuasive because the applicant does not argue the rejection for claim 85. Instead, applicant amended claims 1, 3, 4, 5, 6, 88, and 89 to specifically recite DNA oligonucleotides. Therefore, the rejection remains for the reasons set forth under the 112 first paragraph enablement rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 7-11, 13-17, 19, 51, 52, 57, 58, 69, 71, 72, 93, 106, 107, and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: how to topically administer a composition to melanocytes if they are not part of a mammal. Suggest

adding the phrase -- of a mammal -- on line 2 of the claim after the word melanocytes. Claims 8-11, 13, 14-17, and 19 are rejected because they are dependent from claims 7 and 14.

Claims 51, 57, 69, and 106 recite the limitation "said oligonucleotides" on line 4 of claims 51, 57, 69, 106 and line 2 of claim 107. There is insufficient antecedent basis for this limitation in the claim.

Claim 52 is rejected because it is dependent on claim 51. Claim 58 is rejected because it is dependent on claim 57. Claim 107 is rejected because it is dependent on claim 106.

Claim 71 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: how to topically administer a composition to epidermal cells if they are not part of a mammal. Suggest adding the phrase -- of a mammal -- on line 2 of the claim after the word cells. Claim 72 is rejected because it is dependent on claim 71.

Claim 93 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: how to topically administer a composition to epidermal cells if they are not part of a mammal. Suggest adding the phrase -- of a mammal -- on line 2 of the claim after the word epidermal cells.

Claim 110 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: how to topically administer a composition to epidermal melanocytes if they are not part of a mammal. Suggest adding the phrase -- of a mammal -- on line 2 of the claim after the word melanocytes.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11, 13-17, 19, 20, 23, 25, 26, 29, 32, 51, 52, 57, 58, 69, 71, 72, 75-79, 81-83, 85, 86, 88, 89, 93-95, 98-107, and 110-113.are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-63 of copending Application No. 10/122,633. Although the conflicting claims are not identical, they are not patentably distinct from each other because each

application embraces using an oligonucleotide for treating a hyperproliferative disorder in a mammal, wherein the oligonucleotide is 2-200 nucleotides in length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments, filed 12/15/03, with respect to claim objection have been fully considered and are persuasive. The objection of claim 2 has been withdrawn because of the amendment to claim 1.

Applicant's arguments, filed 12/15/03, with respect to claim objection have been fully considered and are persuasive. The objection of claim 16 has been withdrawn because of the terminal disclaimer filed to overcome the double patenting rejection for claim 14.

Applicant's arguments, filed 12/15/03, with respect to 112 first paragraph have been fully considered and are persuasive. The rejection of claims 63, 64, 108, and 109 has been withdrawn because of the cancellation of the claims.

Applicant's arguments, filed 12/15/03, with respect to 112 second paragraph have been fully considered and are persuasive. The rejection of claims 77-79 and 81 has been withdrawn because of the amendment of the claims.

Applicant's arguments, filed 12/15/03, with respect to double patenting rejection over US 5,643,556 have been fully considered and are persuasive. The rejection of claims 1, 3, 5, 6, 8, 14, 15, 17, 19, and 93 has been withdrawn because of the terminal disclaimer filed over 5,643,556.

Applicant's arguments, filed 12/15/03, with respect to double patenting rejection over US 5,532,001 have been fully considered and are persuasive. The rejection of claims 1, 3, 6, 14, 15, 19, and 93 has been withdrawn because of the terminal disclaimer filed over US 5,532,001.

Applicant's arguments, filed 12/15/03, with respect to double patenting rejection over 5,580,547 have been fully considered and are persuasive. The rejection of claims 8, 14, 15, 19, and 93 has been withdrawn because of the terminal disclaimer filed over US 5,580,547.

Applicant's arguments, filed 12/15/03, with respect to double patenting rejection over 5,470,577 have been fully considered and are persuasive. The rejection of claims 14, 15, 19, and 93 has been withdrawn because of the terminal disclaimer filed over 5,470,577.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the

Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER